Amendments to the Drawings:

Please replace Figure 2 with the replacement sheet for Figure 2, attached herewith in the Appendix. Figure 2 has been amended in response to the Examiner's objection so that the signature sequence shown in bold is clear and easy to distinguish.

Attachment: Replacement Sheet

REMARKS

Status of the Claims

Responsive to the Restriction Requirement mailed April 16, 2003, claims 7-9, 12, 17-18, 21-22, 24-26, and 29 have been canceled without prejudice to, or disclaimer of, the subject matter contained therein. Claims 1, 3, 6, 10, 11, 13, 14, 15, 19, 20, 23, and 27 have been amended and new claims 30-33 have been added, as described elsewhere herein. Support for the amendments and new claims can be found in the original claims or in the specification, as described herein below. Therefore, no new matter has been added by amendment.

Claims 1-6, 10, 11, 13-16, 19, 20, 23, 27, 28, and 30-33 are now pending. The Examiner's comments are addressed below in the order set forth in the Office Action.

Objection to the Specification

The Examiner objects to the specification for containing embedded hyperlinks. Responsive to the Examiner's objection, the specification has been amended to remove the "http://" required to embed the link, thereby obviating the objection.

Objection to the Claims

The Examiner objects to claims 14, 15, and 23 for depending upon non-elected claims. The claims have been amended to correct dependency, thereby obviating the objection.

The Rejections of the Claims under 35 U.S.C. § 101 Should Be Withdrawn

Claims 1-6, 10, 11, 13-16, 19, 20, 23, 27, and 28 stand rejected under 35 U.S.C. § 101. These rejections are respectfully traversed.

The Office Action alleges that Applicant's assignment to the family of MLH1 mismatch repair polypeptides does not establish a satisfactory utility. In particular, the Office Action relies upon a statement in Jean *et al.* (1999) *Mol. Gen. Genet.* 262:633-642 and notes that Applicant has not set forth mutant analysis for the claimed polypeptide. As explained in the following paragraphs, these grounds are insufficient to support the present rejection.

It is not the applicant's burden to establish utility unless the Examiner shifts the burden by establishing, with evidence, that one of skill in the art would doubt the asserted utility. *In re Brana*, 34 U.S.P.Q.2d 1437, 1441 (Fed. Cir. 1995)("Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the Applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility."). The Office Action cites the statement in Jean *et al.* found on page 641, 2nd paragraph: "Despite obvious similarities between *AtMLH1* and its counterparts in other eukaryotes, definite proof that *AtMLH1* plays a role in MMR [mismatch repair] in *Arabidopsis* can only be obtained through mutant analysis." Based on this statement, the Office Action reasons that Applicant "provides no such mutant analysis" and concludes that utility has not been established. However, the Federal Circuit has emphasized that "a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' is sufficient." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 USPQ2d 1895, 1900 (Fed. Cir. 1996). Thus, rigorous correlation through mutant analysis is not necessary to confirm utility for Applicant's claimed sequences.

Moreover, the statement of Jean *et al.* does not constitute a showing that one of ordinary skill in the art would reasonably doubt a homology-based functional assignment without information gained from mutant studies. Indeed, the mutant studies of Jean *et al.* failed to yield a disrupted *AtMLH1* or any data related to disrupted function. Nonetheless, Jean *et al.* titled their journal article "Isolation and characterization of *AtMLH1*, a *MutL* homologue from *Arabidopsis thaliana*." In the abstract, Jean *et al.* state "Using degenerate primers, we have cloned the first plant homologue of the *E. coli MutL gene*...." See page 634. Jean *et al.* further state, "In the work reported here, we describe the isolation and initial characterization of the *Arabidopsis MLH1* gene, the first *MutL* homologue identified in plants." See page 634, first paragraph. These statements exhibit certainty on the part of Jean *et al.* that they have identified a *MLH1* gene from *Arabidopsis despite the lack of any informative mutant analysis.* Applicant notes that the Jean *et al.* reference is peer-reviewed. Accordingly, one of skill in the art would not doubt a functional assignment based upon sequence homology, regardless of whether mutant analysis has been carried out.

In the present case, Applicant has demonstrated robust homology between the novel *MLH1* sequences of the invention and the *Arabidopsis MLH1* sequence. See Figures 3 and 4. Figure 3 shows an alignment of the rice *MLH1* amino acid sequence (SEQ ID NO:2) (top strand) with that of the Arabidopsis thaliana *MLH1* (SEQ ID NO:4). These proteins display 74.4% similarity and 66.6% identity. Figure 4 shows an alignment of the nucleotide sequence of rice *MLH1* cDNA (SEQ ID NO:1) (top strand) with that of the A. thaliana *MLH1* (Accession No. AJ012747; SEQ ID NO:3). Overall, these sequences are 67.9% identical as determined by the BESTFIT program of GCG. In addition, Applicant has disclosed the MutL signature sequence for the rice *MLH1* sequence. See Figure 2 (MutL sequence in bold). Therefore, one of skill in the art would not doubt that Applicant's claimed sequences are *MLH1* sequences. Such sequences have a well-established utility in increasing the efficiency of targeted gene mutation and homologous recombination through the inhibition of the DNA mismatch repair system. See the specification, page 4, lines 17-29, page 5, lines 24-27 and page 6, *et seq.*

The Office Action analogizes to *Brenner v. Manson,* 383 U.S. 519, 148 U.S.P.Q. 689 (1966). *Brenner* is distinguishable, however. In the broadest holding that may be ascribed to it, *Brenner* held that an invention must have "substantial utility," *i.e.*, "specific benefit exist[ing] in currently available form." 148 U.S.P.Q. at 695. Even this broad standard is satisfied by the uses disclosed for the present invention. Thus, one of skill in the art would not doubt that Applicant's invention satisfies the statutory standards for utility.

As further evidence that the presently disclosed sequences are *MLH1* sequences, Applicant submits herewith an alignment between SEQ ID NO:2 and the PFAM domain sequence for the DNA mismatch repair family of proteins, as well as the PFAM description for the DNA mismatch repair domain. See **Exhibit A**, submitted concurrently herewith. As is known in the art, the publicly available PFAM database provides a curated collection of well-characterized protein family domains with high quality alignments and functional domains of novel proteins may be identified by comparison with the PFAM protein family domain alignments. See, e.g., Sonhammer *et al.* (1997) *Proteins* 28(3):405-420. It is well known in the art that regions of sequence homology with known functional domains may be used to determine protein function. For instance, genome projects have used PFAM extensively for large scale

functional annotation of genomic data. See Bateman *et al.* (2002) *Nucleic Acids Res.* 30:276-280, submitted herewith as **Exhibit B**. Thus, the presence of a PFAM DNA mismatch repair domain consensus sequence constitutes strong scientific evidence that SEQ ID NO:2 functions as a *MLH1* protein.

In summary, the assertion that Jean *et al.* demonstrates that those of skill in the art would not accept a functional assignment based upon homology is incorrect. No other evidence is submitted in support of the present rejection and, for this reason alone, it should be withdrawn. Further, Applicant has submitted additional evidence from the publicly available PFAM database demonstrating that the disclosed sequence is an *MLH1* polypeptide. Such sequences possess substantial and well-established utility. Accordingly, the rejection of claims 1-6, 10, 11, 13-16, 19, 20, 23, 27, 28 under Section 101 should be withdrawn and should not be applied to the new claims or the claims as amended.

The Rejections of the Claims under 35 U.S.C. § 112, First Paragraph Should Be Withdrawn

Claims 1-6, 10, 11, 13-16, 19, 20, 23, 27 and 28 stand rejected under 35 U.S.C. § 112, first paragraph, enablement. The rejection of these claims is respectfully traversed.

The Office Action asserts that one of skill in the art would not be able to use the present invention on the grounds that utility has not been established. In particular, the Office Action reiterates that no mutant studies are disclosed. As explained in the preceding section of this response, the sequence homology and presence of conserved domain(s) disclosed in the present application is sufficient to satisfy those of skill in the art that Applicant's sequence is a *MLH1* sequence. This is all that is required to satisfy the patent statute. The Federal Circuit has cautioned against applying standards other than those required by Section 101 and 112 of the patent statute. *In re Brana*, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995)(overturning the PTO's Section 112 rejection on the grounds that an incorrectly rigorous standard had been applied). To the extent the present rejection is based upon an assertion that Applicant's disclosed sequence does not encode a *MLH1* protein, is not involved in mismatch repair, or lacks utility, the present rejection should be withdrawn.

The Office Action also cites *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and mentions the *Wands* factors. In particular, the Office Action asserts that undue experimentation would have been required to "definitively establish that the polypeptide encoded by SEQ ID NO:1 is a MLH1 polypeptide." It further reiterates its position that Jean *et al.* teaches that "one of skill in the art cannot presume that just based on sequence similarity, that a polypeptide has a specific function...." For the reasons already described, this position is not accurate. The Office Action also alleges that Applicant has provided "no evidence of the function of the polypeptide encoded by SEQ ID NO:1." To the contrary, Applicant has demonstrated robust homology between the novel *MLH1* sequences of the invention and the *Arabidopsis MLH1* sequence. See Figures 3 and 4. The Office Action further states that "a structural-functional relationship had not been established by the art at the time of Applicant's invention." This is not the case. A structure-function was established in the art for *MLH1* sequences by the time of Applicant's invention. This relationship is set forth in the background of Applicant's disclosure:

> Many of the mismatch repair genes and the pathways they participate in are also conserved in eukaryotic organisms (Nickoloff and Hoeskstra (1998) *DNA Damage and Repair, Vol. I-II* (Humana Press, New York); Muster-Nassal and Kolodner (1986) *Proc. Natl. Acad. Sci. USA* 83:7618-7622). Yeast *PMS1* was one of the first eukaryotic mismatch repair genes to be isolated and shown to be an ortholog of bacterial *mutL* (Kramer *et al.* (1989) *J. Bacteriol.* 171:5359-5346). The genome of the yeast *Saccharomyces cerevisiae* has been completely sequenced and contains a total of four *mutL* homologs (Flores-Rozas and Kolodner (1998) *Proc. Natl. Acad. Sci.* 95:12404-12409. Orthologs of *mutL* have also been isolated from mouse (Edelmann *et al.* (1996) *Cell* 85:1125-1134), human (Bronner *et al.* (1994) *Nature* 368:258-261), and rat (Geeta *et al.* (1999) *Genomics* 62:460-467). In humans, three *mutL* homologs have been cloned (*MLH1, PMS1, and PMS2*) (Bronner *et al.* (1994) *Nature* 368:258-261; Nicolaides *et al.* (1994) *Nature* 371:75-80; Papadopoulos *et al.* (1994) *Science* 263:1625-1629).
>
> Less is known about the mismatch repair system in plants. Four *Arabidopsis thaliana mutS* homologs have been reported (*AtMSH2, AtMSH3, AtMSH6-1, and AtMSH6-2*) (Culigan and Hays (1997) *Plant Physiol.* 115:833-839; Ade *et al.* (1999) *Mol. Gen. Genet.* 262:239-249) and, as has generally been the case in other eukaryotes, this suggests that plants similarly possess gene families whereas prokaryotes rely on a single gene. Recently, Jean *et al.* reported

> the cloning and characterization of the first plant *mutL* ortholog from *Arabidopsis thaliana* (*AtMLH1*) (Jean *et al.* (1999) *Mol. Gen. Genet* 262:633-342).
>
> The sequence conservation of the *mutL* orthologs of bacteria, yeast, and mammals has facilitated the characterization of the principle players involved in this important mismatch repair pathway.

See the specification, page 2, line 11 to page 3, line 5.

The Office Action further rejects Applicant's genus claims drawn to "nucleotide sequences that hybridize to" or have "about 75% sequence identity to" the nucleotide sequence "shown in SEQ ID NO:1" or "to the cDNA insert of the plasmid deposit PTA-2021," asserting that Applicant has provided no guidance on how to make and use such nucleic acids. Claims 4 and 5, drawn to fragments of SEQ ID NOS:1 and 2 are rejected for similar reasons.

Applicant notes that claims 1-3, 6, 10, 11, 13-16, 19, 20, 23, 27 and 28 as amended no longer recite "nucleotide sequences that hybridize to" or have "about 75% sequence identity to" the nucleotide sequence "shown in SEQ ID NO:1" or "to the cDNA insert of the plasmid deposit PTA-2021." Accordingly, the present rejection of claims 1-3, 6, 10, 11, 13-16, 19, 20, 23, 27 and 28 should be withdrawn.

New claims 30-33 have been added. These claims are drawn to sequences with a 85% or greater identity to the presently claimed sequences and nucleotide sequences that hybridize to the disclosed sequences. However, these new claims specify that the polypeptides recited in these claims or encoded by the nucleotide sequences recited in these claims have mismatch repair activity. Support for the subject matter of the new claims can be found in original claim 1, as well as in the specification at page 8, line 20 and page 22, lines 19-24. As is recognized in the art, the variants and fragments of claims 4, 5, and 30-33 can be generated from the sequences of the invention in various ways, including amino acid substitutions, deletions, truncations, insertions, and other mutagenesis techniques. Guidance is included in the specification for using these sequences, as well. See the specification, page 21, lines 7-23 and page 24, line 27 to page 26, line 27.

Contrary to the statements in the Office Action, guidance is provided in Applicant's disclosure for altering the sequences of the invention. See the specification, page 9, lines 2-14,

describing standard mutagenesis techniques. Further, guidance regarding conservatively modified sequences is provided in the present disclosure. See the specification, page 7, line 14 to page 10, line 11 (describing variants and fragments). By reference to a standard codon table, one of skill in the art could predict which modifications would be tolerated. Applicant has also disclosed the MutL signature sequence for the rice *MLH1* sequence, as well as an alignment between the sequences for Applicant's rice *MLH1* sequence and the *Arabidopsis MLH1* sequence. See Figures 2, 3 and 4. By aligning these sequences, one of skill in the art can determine conserved regions unlikely to tolerate mutation or truncation. Finally, art recognized screening assays for mismatch repair are set forth in the specification on page 9, lines 22-26.

Thus, a rational scheme for determining the regions of the recited *MLH1* sequences that would tolerate modification is provided. Based on the guidance regarding the consensus signature sequences of the *MLH1* polypeptide, and the methods for identifying additional residues critical for mismatch repair activity, the skilled artisan could choose among possible modifications to produce polypeptides within the parameters set forth in the claims and then test these modified variants to determine if they retain mismatch repair activity.

Applicant emphasizes that it is now customary in the art to make a number of sequences and to test them in a large-scale assay for a desired function. Consequently, such experimentation is not "undue." For example, routine experiments involve what is commonly referred to as "shuffling," as described for example in U.S. Patent No. 5,837,458, issued November 17, 1998 with inventors Minshull and Stemmer and entitled, "Methods and Compositions for Metabolic and Cellular Engineering." The art contains many examples of the use of such techniques. Thus, other publications such as Minshull and Stemmer (1999) *Current Opinion in Chemical Biology* 3:284-290 and Christians *et al.* (1999) *Nature Biotechnology* 17: 259-264 demonstrate that experiments comprising shuffling and large-scale functionality assays are now considered routine in the art. Because such experiments are routine, they would not be considered "undue experimentation" under *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Thus, the rejection of claims 4 and 5 should be withdrawn and the present rejection should not be applied to new claims 30-33.

In summary, the practice of the claimed subject matter does not require undue experimentation. The present rejection under Section 112, first paragraph, enablement, should be withdrawn and should not be applied to the new claims or the claims as amended.

The Rejections Under 35 U.S.C. § 112, First Paragraph, Written Description, Should be Withdrawn

Claims 1-6, 10, 11, 13-16, 19, 20, 23, 27, and 28 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of an adequate written description. This rejection is respectfully traversed.

The Office Action asserts that Applicant does not describe the function of the disclosed sequences and cites Jean *et al.* for support. Further, the Office Action recites MPEP § 2163 for the principle that a sequence cannot be described solely by function. For the reasons already set forth above, Applicant's sequence homology establishes SEQ ID NOS:1 and 2 as *MLH1* sequences to the satisfaction of those of skill in the art. Further, Applicant has disclosed the actual structure of SEQ ID NOS:1 and 2 and does not rely solely upon a functional description. As explained below, Applicant's disclosure is sufficient to satisfy the statutory standard for written description.

First, Applicant makes reference in the specification to the plasmid containing the cDNA insert corresponding to SEQ ID NO:1 (PTA-2021). Reference in the specification to a deposit in a public depository satisfies the written description requirement. *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 63 U.S.P.Q.2d 1609 (Fed. Cir. 2002). The sequence listing sets forth the actual structure of SEQ ID NOS: 1 and 2. A description can be by structure, formula, chemical name, or physical properties. *See Ex parte Maizel*, 27 USPQ2d 1662, 1669 (B.P.A.I. 1992), *citing Amgen v. Chugai*, 927 F.2d 1200, 1206 (Fed. Cir. 1991). As amended, claims 1-6, 10, 11, 13-16, 19, 20, 23, 27, and 28 are drawn to these sequences. Thus, the subject matter of claims 1-6, 10, 11, 13-16, 19, 20, 23, 27, and 28 satisfies the written description requirement and the rejection of these claims should be withdrawn. Further, the rejection should not be applied to new claims 30-33, as explained in the following paragraphs.

New claims 30-33 are drawn to a genus of DNAs. Such a genus may be described by means of a recitation of a representative number of DNAs, defined by nucleotide sequence, falling within the scope of the genus, *or* by means of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997); *see also* Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (2001). An Applicant may also rely upon functional characteristics in the description, provided there is a correlation between the function and structure of the claimed invention. *Id.*, *citing Lilly* at 1568.

Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. 66 Fed. Reg. 1099, 1106 (2001). Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. 66 Fed. Reg. 1099, 1106 (2001).

New claims 30-32 recite nucleotide sequences having at least 85% sequence identity to the sequence set forth in SEQ ID NO:1 (or the cDNA insert of PTA-2021). The recitation of at least 85% sequence identity is a *very predictable structure* of the sequences encompassed by the claimed invention. Further, claims 30-32 specify that the encoded polypeptide have mismatch repair activity, thereby providing a functional characterization of the sequences claimed in the genus. As discussed above, there is an art-recognized correlation between *MLH1* sequences and the family of mismatch repair enzymes. Given SEQ ID NO:1 as a representative species, the functional characterization of the sequences claimed, and the knowledge and level of skill in the art, a person of ordinary skill could envision the claimed invention, *i.e.*, a sequence having at least 85% sequence identity to the sequence set forth in SEQ ID NO:1 (or the cDNA insert of PTA-2021).

Applicant cites Example 14 of the Revised Interim Written Description Guidelines in support of the present traverse. Example 14 is directed to a generic claim: a protein having at least 95% sequence identity to the sequence of SEQ ID NO:3, wherein the sequence catalyzes

the reaction A → B. The Training Materials concludes that the generic claim of Example 14 is sufficiently described under § 112, first paragraph, because 1) "the single sequence disclosed in SEQ ID NO:3 is representative of the genus" and 2) the claim recites a limitation requiring the compound to catalyze the reaction from A → B. The Guidelines conclude that one of skill in art would recognize that the Applicants were in possession of the necessary common attributes possessed by the members of the genus.

Following the analysis of Example 14, Applicants submit that new claims 30-32 satisfy the written description requirements of § 112, first paragraph. Specifically, the claims of the present invention encompass sequences having at least 85% sequence identity to the sequence of SEQ ID NO:1 wherein the claimed sequence encodes a polypeptide having mismatch repair activity. As in Example 14, the specification discloses the nucleic acid sequence of SEQ ID NO:1, and the amended claims recite a limitation requiring the compound to have a specific function (*i.e.*, a mismatch repair activity).

Consequently, contrary to the conclusion of the Office Action, the sequences encompassed by the genus claims of claims 30-32 are defined by relevant identifying physical and chemical properties. Therefore, claims 30-32 satisfy the written description standard.

Similarly, claim 33 recites a genus of nucleotide sequences that hybridize under stringent conditions to SEQ ID NO:1 or its complement. As those of skill in the art are aware, whether or not a nucleic acid molecule will hybridize under specified stringency conditions is determined by the nucleic acid composition and sequence, i.e., its structure. See, e.g., Ausubel *et al.*, *Current Protocols in Molecular Biology*, John Wiley & Sons (1998). The necessary common features of the claimed genus are clear.

In summary, the description of a representative number of species *does not* require the description to be of such specificity that it would provide individual support for each species that the genus embraces. Applicants submit that the relevant identifying physical and chemical properties of the disclosed genus would be clearly recognized by one of skill in the art and consequently, the Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus. Accordingly, the rejection of claims 1-6,

10, 11, 13-16, 19, 20, 23, 27, and 28 under 35 U.S.C. §112, first paragraph, for lack of written description should be withdrawn and not applied to the newly submitted claims.

The Rejections Under 35 U.S.C. § 112, Second Paragraph, Should be Withdrawn

Claims 1-3, 6, 10, 11, 13-16, 19, 20, 23, 27, and 28 stand rejected under 35 U.S.C. § 112, second paragraph. This rejection is respectfully traversed.

The rejection is founded on the recitation of "hybridizes...under stringent conditions" in these claims (or the claims from which they depend). However, as amended, these claims no longer recite (or depend from a claim that recites) "hybridizes...under stringent conditions." Thus, the Examiner's concerns are alleviated and the rejection should be withdrawn.

Further, the rejection should not be applied to new claim 33. Although the claim recites hybridization, it specifies that "stringent conditions comprise hybridization in 50% formamide, 1 M NaCl, 1% SDS at 37°C, and a wash in 0.1X SSC at 60 to 65°C." Support for the recited conditions can be found at page 12, lines 21-24. Because the claim recites specific stringent conditions, the Examiner's concerns are obviated.

Claim 6 stands rejected under 35 U.S.C. § 112, second paragraph. As suggested by the Examiner, the claim has been amended to recite "the isolated nucleic acid molecule" to obviate the rejection. Accordingly, the rejection should be withdrawn. Applicant thanks the Examiner for the helpful suggestion.

Claim 23 stands rejected under 35 U.S.C. § 112, second paragraph. In particular, the Office Action asserts that the phrase "a transgenic plant" is intended by the recited phrase "a hybrid plant species," citing page 29 of the specification. This rejection is respectfully traversed.

The recited language, "a hybrid plant species," is explained in the paragraph spanning pages 20-21, as follows:

> The present invention takes advantage of the important roles of the MLH1 proteins in mismatch repair, recombination, and meiotic processes. One aspect of the present invention is directed to the inhibition of either the expression or the

> activity of MLH1 proteins in plants, to impair the cellular mismatch repair system and consequently encourage genetic modifications through increased rates of mutagenesis and non-specific recombination events. For example, the methods of the present invention that are directed to the inhibition of the plant cellular mismatch repair system have use in increasing the efficiency of the method of genetic modification known as chimeraplasty (See, U.S. Patent Nos. 5,565,350; 5,731,181; 5,756,325; 5,760,012; 5,795,972; and 5,871,984; all of which are herein incorporated by reference) and described herein *infra*. In this manner, it is also an object of the invention to facilitate the formation of novel hybrid species, or more specifically, novel hybrid genes or enzymes by *in vivo* intergeneric and/or interspecific recombinations. Sense and antisense oligonucleotides, antibodies, peptides, transposons, site-directed mutagenesis, ribozymes, and the like may be utilized to inhibit the mismatch repair activity of MLH1 proteins. Because mismatch repair mutants may be genetically unstable, it may be advantageous to use a transient inhibition of the mismatch repair system for only as long as necessary to construct the desired genetic modification, and then restore the system to normal. The present invention provides methods for such a transient inhibition of the cellular mismatch system.

Applicant submits that the language "a hybrid plant species" found in claim 23 does not have the same meaning as "a transgenic plant," as demonstrated by the paragraph quoted from the disclosure. Thus, the Examiner's concern that Applicant has defined a claim term contrary to its ordinary meaning is alleviated and the rejection of claim 23 should be withdrawn accordingly.

The Rejections Under 35 U.S.C. § 102 Should be Withdrawn

Claims 1-3, and 6 stand rejected as anticipated under 35 U.S.C. § 102. This rejection is respectfully traversed.

The rejection is founded on the recitation of "hybridizes...under stringent conditions" in these claims (or the claims from which they depend). Specifically, the Office Action asserts that the sequences of these claims would hybridize to the sequence of Prolla *et al.* (1994) *Science* 265:1091-3. However, as amended, these claims no longer recite (or depend from a claim that recites) "hybridizes...under stringent conditions." Thus, the Examiner's concerns are alleviated and the rejection of claims 1-3 and 6 should be withdrawn.

Further, the present rejection should not be applied to new claim 33 which specifies that "stringent conditions comprise hybridization in 50% formamide, 1 M NaCl, 1% SDS at 37°C, and a wash in 0.1X SSC at 60 to 65°C." Applicant's representative diligently searched the Prolla *et al.* reference, but was not able to determine what sequence was utilized therein, nor was the present rejection accompanied by an alignment of the Prolla *et al.* sequence with Applicant's sequence. Absent a definite sequence, the Office cannot carry its burden of establishing anticipation. For this reason, the present rejection should not be applied to new claim 33.

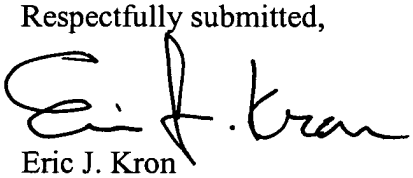
CONCLUSION

In view of the aforementioned amendments and remarks, Applicant respectfully submits that the objection to the specification and the rejections of the claims under 35 U.S. C. §§ 101, 102, and 112 are overcome. Accordingly, Applicant submits that this application is now in condition for allowance. Early notice to this effect is solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



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Nora C. Martinez